REMARKS

Supplemental Information Disclosure Statement filed June 2003 with Previous Response

In the Supplemental IDS and accompanying Form PTO-1449 submitted by Applicants with the June 2003 Response, Applicants cited a reference (WO 01/66736), a copy of which had previously been submitted with the March 2003 IDS. The Office Action of November 2003 states that the citation of this reference was crossed out on the Form PTO-1449, and would not be considered because "the Examiner does not read Japanese, thus in order to consider the WO 01/66736, it has to be translated to English" (Office Action, page 2, item 3). For the reasons submitted below, Applicants respectfully request that the reference be considered and made of record.

Section 609 of the MPEP, particularly at section 609 III A(2) and section 609 III A(3) on page 600-122, describes the procedure for consideration of references submitted by Applicants that are not in the English language. Applicants are not required to submit a translation of a non-English language reference unless they have such a translation:

> Translations are not required to be filed unless they have been reduced to writing and are actually translations of what is contained in the non-English language information. If no translation is submitted, the examiner will consider the information in view of the concise explanation and insofar as it is understood on its face, e.g., drawings, chemical formulas, English language abstracts, in the same manner that non-English language information in Office search files is considered by examiners in conducting searches. (MPEP, section 609 III A(2))

In the June 2003 Response, it was indicated that Applicants have not had a translation made of WO 01/66736, therefore Applicants are not required to submit a translation of this reference in order to have the reference made of record and considered by the Examiner (see 37 CFR 1.98(a)(3)(ii)).

Applicants have submitted a copy of the WO 01/66736 reference with the March 2002 IDS; they have properly cited the WO 01/66736 reference on the Form PTO-1449 submitted with the June 2003 Response; and they have provided a concise explanation of the relevance of the non-English language information contained in the WO 01/66736 reference (see 37 CFR 1.98(a)(3)(i)). In the Supplemental IDS submitted with the June 2003 Response, Applicants provided a concise explanation of the relevance of the WO 01/66736 reference by stating that the WO 01/66736 reference was submitted because it discloses murine nectin-3

polypeptides. In addition, in the June 2003 Response, Applicants respectfully directed the Examiner's attention to the EP 1179592 A and US 2003/0008334 A1 references as "publications in the English language of the European and US applications, respectively, corresponding to the WO 01/66736 PCT publication ... [t]hese publications (EP 1 179 592 A and US 2003/0008334 A1) each appear to be a translation of the WO 01/66736 publication into English". According to the MPEP, providing the corresponding EP or US English-language publications of non-English applications is another way to provide the concise explanation of 37 CFR 1.98(a)(3)(i):

> **A (3) Concise Explanation of Relevance for Non-English Language Information**
> ... An English-language equivalent application may be submitted to fulfill this requirement if it is, in fact, a translation of a foreign language application being listed in an information disclosure statement. There is no requirement for the translation to be verified. (MPEP, section 609 III A(3))

Therefore, Applicants have complied with all of the requirements of 37 CFR 1.98 for submission of the WO 01/66736 reference, and consideration of this reference by the Examiner is respectfully requested. For the convenience of the Examiner, Applicants submit herewith a clean copy of the Form PTO-1449 submitted with the June 2003 Response.

Amendments to the Specification

In the June 2003 Response, Applicants submitted amendments to the paragraph beginning at page 6, line 15 and to Table 2 which begins at page 7, line 7. The October 2003 Office Action objected to these amendments on the basis that they introduced new matter; although Applicants do not accede to the basis for the objection, Applicants have in the present amendments submitted a replacement paragraph and Table. The present amendments do not include new matter.

With respect to the paragraph beginning at page 6, line 15, the present amendment restores this paragraph to its text as originally filed.

Table 2 as originally filed in the specification had a consensus sequence that included both capitalized letters and lower-case letters. The paragraph at page 6, line 15 indicates that the capitalized letters are consensus residues that are identical among at least a majority of the amino acid sequences in the alignment. The text of the specification does not describe the lower-case letters of the Table 2 consensus sequence in particularity, and their presence in the Table 2 consensus sequence may make it more difficult to read: for example, a lower-case 'v'

might easily be mistaken for a capital 'V'. The present amendment clarifies Table 2 by removing the lower-case letters from the consensus sequence; removing these characters does not introduce new matter. In addition, the present amendment to Table 2 corrects typographical errors so that the capitalized letters in the consensus sequence are consistent with the description of these capitalized letters in the paragraph at page 6, line 15: capital letters are now included in the Table 2 consensus sequence at every position where three or more of the five amino acid sequences in the alignment share amino acid identity. This correction of typographical errors in the Table 2 consensus sequence does not introduce new matter, and clarifies the presentation of the information of Table 2 for the benefit of the public. For the Examiner's convenience, an additional 'clean' copy of Table 2 is presented in Appendix A.

For at least the above reasons, the Examiner is respectfully requested to withdraw the objection to the amendments to the specification.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 60, 67, 73-78, and 105 were rejected under 35 U.S.C. §112, first paragraph, as being considered to contain matter that was not described in the specification. Applicants respectfully traverse the grounds for this rejection for at least the following reasons.

The Office Action at page 3, item 9, identifies nine phrases (labeled for convenience **A** through **I**) as representing "a departure from the specification and the claims as originally filed". Applicants will indicate in the following paragraphs that the specification contains support for each of these phrases.

A. and **B.** Because the following description of support for the phrases labeled 'A' is similar to that for the phrases labeled 'B', these items will be discussed together.

A. Claim 60 (a): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:4 or 6;

Claim 60 (b): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:13; and

Claim 60 (c): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:15.

B. Claim 67 (a): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:10 or 12;

Claim 67 (b): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:14;

Claim 67 (c): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:16; and

Claim 67 (d): an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:31.

The above phrases refer to amino acid sequences of polypeptides from which signal sequence residues have been removed. The signal sequence for the nectin-3 polypeptides is described at page 4 of the specification, line 39 through page 5, line 5 (emphasis added):

> The signal sequence for nectin-3α, β, or γ is located and begins between about amino acid 1 to 39 and extends to about amino acid 57 (*e.g.*, from x_1 to about 57, wherein x_1 is an amino acid between 1 and 39) of SEQ ID Nos: 6, 12, and 31, *with the mature polypeptide formed by cleavage following the signal sequence*. Typically the signal sequence is cleaved following amino acid 50, 55, or 57, depending upon factors such as the host cell used. *Accordingly, the mature polypeptide comprises an amino acid sequence starting at an amino acid between, and including, residue 51 and 58 (e.g., at amino acid 51, 52, 53, 54, 55, 56, 57, or 58;) of SEQ ID Nos: 6, 12, and 31.*

The above provides support for mature polypeptides extending from amino acid 58 of SEQ ID NO:6 through its C-terminus, and from amino acid 58 of SEQ ID NO:12 through its C-terminus, and from amino acid 58 of SEQ ID NO:31 through its C-terminus.

SEQ ID NO:4 and SEQ ID NO:6 differ from each other only at amino acid positions 5 and 6 (see page 6, line 38, through page 7, line 4, of the specification, and the Sequence Listing), therefore an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:4 is identical to an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:6. Similarly, SEQ ID NO:10 and SEQ ID NO:12 differ from each other only at amino acid positions 5 and 6 (see page 6, line 38, through page 7, line 4, of the specification, and the Sequence Listing), therefore an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:10 is identical to an amino acid sequence extending from amino acid 58 through the C-terminus of SEQ ID NO:12.

The polypeptides of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:16 comprise nectin-3 N-terminal amino acid sequences including nectin-3 signal sequences (page 17, lines 12-17). Polypeptides of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:16 from which the signal sequence has been removed are described at page 7, lines 5-6 and also at page 52, line 23 ("The soluble form of the molecule is then predicted to start at amino acid 58 of SEQ ID NO:13 or 14").

The specification therefore provides support for polypeptides having N-terminal nectin-3 amino acid sequences from which the nectin-3 signal sequence has been removed, resulting in such polypeptides having an amino acid sequence extending from amino acid 58 through the C-terminus of the polypeptide. Phrases A and B as used in claims 60 and 67 do not, for at least these reasons, represent new matter.

C. and **F.** The phrase labeled 'C' is identical to the phrase labeled 'F': "amino acids 58 through 342 of SEQ ID NO:31";

D. and **G.** The phrase labeled 'D' is identical to the phrase labeled 'G': "amino acids 74 through 342 of SEQ ID NO:31";

E. and **I.** The phrase labeled 'E' is identical to the phrase labeled 'I': "amino acids 74 through 365 of SEQ ID NO:31";

H. The phrase labeled 'H' is "amino acids 58 through 365 of SEQ ID NO:31".

Because the following description of support applies similarly to the phrases labeled 'C' through 'I', these items will be discussed together.

As described at page 4, lines 38-39 of the specification: "Nectin-3α, β, and γ are related to each other as the products of alternative splicing: the N-terminal 356 amino acids of the full-length amino acid sequences of these polypeptides are identical." SEQ ID NO:31 is human nectin-3γ (page 4, lines 33-34 and the Table on page 60 of the specification). Therefore, amino acids 1 through 356 of SEQ ID NO:31 are identical to amino acids 1 through 356 of SEQ ID NOs 6 and 12 (human nectin-3α and -3β, respectively). Based on this identity and on the similarity between SEQ ID NOs 4 and 6, and SEQ ID NOs 10 and 12, as discussed above (see page 6, line 38, through page 7, line 4, of the specification), it follows that amino acids 58 through 342 of SEQ ID NO:31 are identical to amino acids 58 through 342 of SEQ ID NOs 4, 6, 10, and 12; and amino acids 74 through 342 of SEQ ID NO:31 are identical to amino acids 74 through 342 of SEQ ID NOs 4, 6, 10, and 12.

As described at page 5, lines 20 through 25 of the specification, nectin-3β (SEQ ID NO:12), and nectin-3γ (SEQ ID NO:31) share additional amino acid sequences, having the same extracellular and transmembrane sequences. Therefore, amino acids 58 through 365 of SEQ ID NO:31 are identical to amino acids 58 through 365 of SEQ ID NOs 10 and 12; and amino acids 74 through 365 of SEQ ID NO:31 are identical to amino acids 74 through 365 of SEQ ID NOs 10 and 12.

These similarities among the nectin-3 polypeptides of the disclosure have been previously presented in a graphical form by Applicants; the Examiner is respectfully directed to the following amino acid alignment, which was submitted by Applicants in October 2002 as part of the Response to the Restriction Requirement:

Alignment of SEQ ID NOs 2, 4, 6, 8, 10, 12, and 31:

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                1                                                   50
NO2   NEC3ALPHA ~~~~~~~~SPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS
NO4   NEC3ALPHA MARTpgPSPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS
NO6   NEC3ALPHA MARTlrPSPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS
NO8   NEC3BETA  ~~~~~~PSPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS
NO10  NEC3BETA  MARTpgPSPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS
NO12  NEC3BETA  MARTlrPSPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS
NO31  NEC3GAMMA MARTlrPSPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS
      Consensus -------SPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS

                51                                                  100
NO2   NEC3ALPHA RLCGALAGPI IVEPHVTAVW GKNVSLKCLI EVNETITQIS WEKIHGKSSQ
NO4   NEC3ALPHA RLCGALAGPI IVEPHVTAVW GKNVSLKCLI EVNETITQIS WEKIHGKSSQ
NO6   NEC3ALPHA RLCGALAGPI IVEPHVTAVW GKNVSLKCLI EVNETITQIS WEKIHGKSSQ
NO8   NEC3BETA  RLCGALAGPI IVEPHVTAVW GKNVSLKCLI EVNETITQIS WEKIHGKSSQ
NO10  NEC3BETA  RLCGALAGPI IVEPHVTAVW GKNVSLKCLI EVNETITQIS WEKIHGKSSQ
NO12  NEC3BETA  RLCGALAGPI IVEPHVTAVW GKNVSLKCLI EVNETITQIS WEKIHGKSSQ
NO31  NEC3GAMMA RLCGALAGPI IVEPHVTAVW GKNVSLKCLI EVNETITQIS WEKIHGKSSQ
      Consensus RLCGALAGPI IVEPHVTAVW GKNVSLKCLI EVNETITQIS WEKIHGKSSQ

                101                                                 150
NO2   NEC3ALPHA TVAVHHPQYG FSVQGEYQGR VLFKNYSLND ATITLHNIGF SDSGKYICKA
NO4   NEC3ALPHA TVAVHHPQYG FSVQGEYQGR VLFKNYSLND ATITLHNIGF SDSGKYICKA
NO6   NEC3ALPHA TVAVHHPQYG FSVQGEYQGR VLFKNYSLND ATITLHNIGF SDSGKYICKA
NO8   NEC3BETA  TVAVHHPQYG FSVQGEYQGR VLFKNYSLND ATITLHNIGF SDSGKYICKA
NO10  NEC3BETA  TVAVHHPQYG FSVQGEYQGR VLFKNYSLND ATITLHNIGF SDSGKYICKA
NO12  NEC3BETA  TVAVHHPQYG FSVQGEYQGR VLFKNYSLND ATITLHNIGF SDSGKYICKA
NO31  NEC3GAMMA TVAVHHPQYG FSVQGEYQGR VLFKNYSLND ATITLHNIGF SDSGKYICKA
      Consensus TVAVHHPQYG FSVQGEYQGR VLFKNYSLND ATITLHNIGF SDSGKYICKA

                151                                                 200
NO2   NEC3ALPHA VTFPLGNAQS STTVTVLVEP TVSLIKGPDS LIDGGNETVA AICIAATGKP
NO4   NEC3ALPHA VTFPLGNAQS STTVTVLVEP TVSLIKGPDS LIDGGNETVA AICIAATGKP
NO6   NEC3ALPHA VTFPLGNAQS STTVTVLVEP TVSLIKGPDS LIDGGNETVA AICIAATGKP
NO8   NEC3BETA  VTFPLGNAQS STTVTVLVEP TVSLIKGPDS LIDGGNETVA AICIAATGKP
NO10  NEC3BETA  VTFPLGNAQS STTVTVLVEP TVSLIKGPDS LIDGGNETVA AICIAATGKP
NO12  NEC3BETA  VTFPLGNAQS STTVTVLVEP TVSLIKGPDS LIDGGNETVA AICIAATGKP
NO31  NEC3GAMMA VTFPLGNAQS STTVTVLVEP TVSLIKGPDS LIDGGNETVA AICIAATGKP
      Consensus VTFPLGNAQS STTVTVLVEP TVSLIKGPDS LIDGGNETVA AICIAATGKP
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                  201                                                 250
NO2   NEC3ALPHA VAHIDWEGDL GEMESTTTSF PNETATIISQ YKLFPTRFAR GRRITCVVKH
NO4   NEC3ALPHA VAHIDWEGDL GEMESTTTSF PNETATIISQ YKLFPTRFAR GRRITCVVKH
NO6   NEC3ALPHA VAHIDWEGDL GEMESTTTSF PNETATIISQ YKLFPTRFAR GRRITCVVKH
NO8   NEC3BETA  VAHIDWEGDL GEMESTTTSF PNETATIISQ YKLFPTRFAR GRRITCVVKH
NO10  NEC3BETA  VAHIDWEGDL GEMESTTTSF PNETATIISQ YKLFPTRFAR GRRITCVVKH
NO12  NEC3BETA  VAHIDWEGDL GEMESTTTSF PNETATIISQ YKLFPTRFAR GRRITCVVKH
NO31  NEC3GAMMA VAHIDWEGDL GEMESTTTSF PNETATIISQ YKLFPTRFAR GRRITCVVKH
      Consensus VAHIDWEGDL GEMESTTTSF PNETATIISQ YKLFPTRFAR GRRITCVVKH

                  251                                                 300
NO2   NEC3ALPHA PALEKDIRYS FILDIQYAPE VSVTGYDGNW FVGRKGVNLK CNADANPPPF
NO4   NEC3ALPHA PALEKDIRYS FILDIQYAPE VSVTGYDGNW FVGRKGVNLK CNADANPPPF
NO6   NEC3ALPHA PALEKDIRYS FILDIQYAPE VSVTGYDGNW FVGRKGVNLK CNADANPPPF
NO8   NEC3BETA  PALEKDIRYS FILDIQYAPE VSVTGYDGNW FVGRKGVNLK CNADANPPPF
NO10  NEC3BETA  PALEKDIRYS FILDIQYAPE VSVTGYDGNW FVGRKGVNLK CNADANPPPF
NO12  NEC3BETA  PALEKDIRYS FILDIQYAPE VSVTGYDGNW FVGRKGVNLK CNADANPPPF
NO31  NEC3GAMMA PALEKDIRYS FILDIQYAPE VSVTGYDGNW FVGRKGVNLK CNADANPPPF
      Consensus PALEKDIRYS FILDIQYAPE VSVTGYDGNW FVGRKGVNLK CNADANPPPF

                  301                                                 350
NO2   NEC3ALPHA KSVWSRLDGQ WPDGLLASDN TLHFVHPLTF NYSGVYICKV TNSLGQRSDQ
NO4   NEC3ALPHA KSVWSRLDGQ WPDGLLASDN TLHFVHPLTF NYSGVYICKV TNSLGQRSDQ
NO6   NEC3ALPHA KSVWSRLDGQ WPDGLLASDN TLHFVHPLTF NYSGVYICKV TNSLGQRSDQ
NO8   NEC3BETA  KSVWSRLDGQ WPDGLLASDN TLHFVHPLTF NYSGVYICKV TNSLGQRSDQ
NO10  NEC3BETA  KSVWSRLDGQ WPDGLLASDN TLHFVHPLTF NYSGVYICKV TNSLGQRSDQ
NO12  NEC3BETA  KSVWSRLDGQ WPDGLLASDN TLHFVHPLTF NYSGVYICKV TNSLGQRSDQ
NO31  NEC3GAMMA KSVWSRLDGQ WPDGLLASDN TLHFVHPLTF NYSGVYICKV TNSLGQRSDQ
      Consensus KSVWSRLDGQ WPDGLLASDN TLHFVHPLTF NYSGVYICKV TNSLGQRSDQ

                  351                                                 400
NO2   NEC3ALPHA KVIYISDpPt ttTlqptiqw hpStadiedl atepkklpFp lstlaTikdd
NO4   NEC3ALPHA KVIYISDpPt ttTlqptiqw hpStadiedl atepkklpFp lstlaTikdd
NO6   NEC3ALPHA KVIYISDpPt ttTlqptiqw hpStadiedl atepkklpFp lstlaTikdd
NO8   NEC3BETA  KVIYISDVPF KQT.......  ..SSIAVAGA VIGAVLALFI IAIFVTVL.L
NO10  NEC3BETA  KVIYISDVPF KQT.......  ..SSIAVAGA VIGAVLALFI IAIFVTVL.L
NO12  NEC3BETA  KVIYISDVPF KQT.......  ..SSIAVAGA VIGAVLALFI IAIFVTVL.L
NO31  NEC3GAMMA KVIYISDVPF KQT.......  ..SSIAVAGA VIGAVLALFI IAIFVTVL.L
      Consensus KVIYISD--- ----------  ---------- ---------- ----------

                  401                                                 450
NO2   NEC3ALPHA TiatiiaSvv ggalfivlvs vlagifcyRr rrtfrgDyF.  ..aknYiPps
NO4   NEC3ALPHA TiatiiaSvv ggalfivlvs vlagifcyRr rrtfrgDyF.  ..aknYiPps
NO6   NEC3ALPHA TiatiiaSvv ggalfivlvs vlagifcyRr rrtfrgDyF.  ..aknYiPps
NO8   NEC3BETA  TPRKKRPSYL DKVIDLPPTH KPPPLYEERS PPLPQKDLFQ  ...pEhlPlq
NO10  NEC3BETA  TPRKKRPSYL DKVIDLPPTH KPPPLYEERS PPLPQKDLFQ  ...pEhlPlq
NO12  NEC3BETA  TPRKKRPSYL DKVIDLPPTH KPPPLYEERS PPLPQKDLFQ  ...pEhlPlq
NO31  NEC3GAMMA TPRKKRPSYL DKVIDLPPTH KPPPLYEERS PPLPQKDLFQ  vcvhEYt~~~

                  451                                                 500
NO2   NEC3ALPHA dmqKEsqidv LQqde.LdSy pdsvkkENkn pvnnlirkdy LeepektQwn
NO4   NEC3ALPHA dmqKEsqidv LQqde.LdSy pdsvkkENkn pvnnlirkdy LeepektQwn
NO6   NEC3ALPHA dmqKEsqidv LQqde.LdSy pdsvkkENkn pvnnlirkdy LeepektQwn
NO8   NEC3BETA  tqfKErevgn LQhsngLnSr sfdyedENpv gedgiqqmyp LynqmcyQdr
NO10  NEC3BETA  tqfKErevgn LQhsngLnSr sfdyedENpv gedgiqqmyp LynqmcyQdr
NO12  NEC3BETA  tqfKErevgn LQhsngLnSr sfdyedENpv gedgiqqmyp LynqmcyQdr

                  501                                                 553
NO2   NEC3ALPHA nvenlnrfer PmdyYeDlkm gmkfvsdehy deneddlvsh vdgsvisrre wyv
NO4   NEC3ALPHA nvenlnrfer PmdyYeDlkm gmkfvsdehy deneddlvsh vdgsvisrre wyv
NO6   NEC3ALPHA nvenlnrfer PmdyYeDlkm gmkfvsdehy deneddlvsh vdgsvisrre wyv
NO8   NEC3BETA  spgkhhqnnd PkrvYiDpre hyv~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~
NO10  NEC3BETA  spgkhhqnnd PkrvYiDpre hyv~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~
NO12  NEC3BETA  spgkhhqnnd PkrvYiDpre hyv~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~
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Support in the specification for amino acids 58 through 342 and amino acids 74 through 342 of SEQ ID NO:31 can therefore be found in references to amino acids 58 through 342 and amino acids 74 through 342 of SEQ ID NO:6 or SEQ ID NO:12, respectively, because these amino acid sequences are the same (see for example the specification at page 1, line 41 and at page 2, line 2 and lines 7-10). Similarly, support in the specification for amino acids 58 through 365 and amino acids 74 through 365 of SEQ ID NO:31 can be found in references to amino acids 58 through 365 and amino acids 74 through 365 of SEQ ID NO:12 (see for example the specification at page 2, lines 8 and 10). For at least these reasons, there is support in the specification for the phrases C through I as used in claims 73 and 105.

Withdrawal of the rejection of claims 60, 67, 73-78, and 105 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 59-111 were rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement.

The Office Action concedes (at the bottom of page 3 of the Office Action) that the specification is enabling for "a substantially purified polypeptide comprising an amino acid [sequence] of SEQ ID NO:2, 4, 6, 8, 10, 12 and 31, wherein SEQ ID NO:4, 6, 10, 12, and 31 compris[e] amino acids 74-152, 189 to 250 and 287 to 342, and SED ID NO: 13-16, wherein the polypeptide consists of amino acid sequence that binds to nectin-1 for inhibiting endothelial cell migration." Given this statement in the Office Action, Applicants can find no basis for applying this rejection to claims 59-78, such claims being directed to polypeptide sequences that have been shown to possess the nectin-1 binding properties referred to (see, for example, Examples 4 through 6 at pages 53-56 of the specification). Applicants respectfully request that the rejection be withdrawn with respect to claims 59-78, or that the Examiner provide the basis for applying the rejection to these claims.

With respect to claims 79-111, the Office Action states grounds for rejection that appear to fall into two general categories: (1) it would purportedly require undue experimentation to produce the number of variants encompassed by the claims; and (2) the claims are considered to not be enabled due to misplaced concerns about the unpredictability of the art. (3) The Office Action also cites *Colbert v. Lofdahl*, but it is unclear how this case

supports the present enablement rejection. These grounds for rejection will be addressed in turn below.

(1). The Office Action, in the second paragraph on page 5 of the Office Action, notes that a large number of variants would have 80% amino acid identity to amino acid sequences such as amino acids 74 through 152, amino acids 189 through 205, or amino acids 287 through 342 of SEQ ID NOs 4, 6, 10, 12, and 31, and expresses a concern that not all of such variations would be "predictive of inhibiting endothelial cell migration", thus requiring a level of experimentation that is "excessive and undue". However, this concern does not consider the *nature* of the experimentation that would be required in using standard techniques, such as those disclosed in the application, to make and test such variants for function. It is well established that routine experimentation, even if it must be performed on numerous variants, does not constitute experimentation that is so undue that it cannot be carried out by those of skill in the art. See, for example, *Ex parte Mark*, 12 U.S.P.Q.2d (BNA) 1904 (BPAI 1989). For at least these reasons, this basis for the rejection of the claims as lacking enablement is inapposite and may properly be withdrawn.

(2). The Office Action, at page 6, cites the Skolnick and Fetrow, Metzler *et al.*, and Martinez *et al.* references for the proposition that the unpredictability of the art would render the skilled artisan unable to make and use the subject matter of the claims. However, as described above, even in the complete absence of any guidance as to which variants of amino acids 74 through 152, amino acids 189 through 205, or amino acids 287 through 342 of SEQ ID NOs 4, 6, 10, 12, and 31 would be functional, the routine experimentation required to make and test such variants would not be so undue as to cause the claimed subject matter to be beyond the skill of the artisan. And as has been conceded by the Office Action at page 5, paragraph 4, Applicants have provided guidance for the production of functional variants.

Further, the references the Office Action relies upon to support the assertion of unpredictability of the art, when read carefully in their entirety, actually demonstrate the fact that the skilled artisan *can* predict which variants are likely to be functional, especially in situations where guidance can be found from comparisons to related polypeptides. These three references, referred to as "Skolnick and Fetrow", "Metzler", and "Martinez", will be discussed further below.

The purpose of Skolnick and Fetrow, 2000, *Trends in Biotech* 18(1): 34-39 is to consider the assignment of biochemical function to proteins generally, based on amino acid sequence and/or on protein three-dimensional structure. Although the article does point out

some limitations in using either sequence information alone or structural information alone (e.g. Box 2 of the article) to predict protein function, the authors also indicate that in many situations sequence-based approaches are *successful* in predicting function from structure. For example, at page 35, column 1 of the article, in the section entitled "Active-site identification", Skolnick and Fetrow state that the approach of using amino acid sequence conservation as an indication of functionally important residues can be a valid one: "these results provide clear evidence that enzyme active sites are indeed more highly conserved than other parts of the protein". Even in Box 2 of their article, relating to the use of three-dimensional protein structure *alone* to predict function, the authors state that "broad function-structure correlations were observed for some structural classes" of proteins. Also, in the section spanning pages 36 and 37, the authors describe successfully combining sequence and structural information to accurately identify proteins with disulfide-oxidoreductase activity, and they conclude at the bottom of the second column on page 37, "[a]lthough **sequence-based approaches to protein-function prediction have proved to be very useful,** alternatives are needed to assign the biochemical function of the *30-50%* of proteins *whose function cannot be assigned by any current method*" (emphasis added). Thus, after a thorough reading of Skolnick and Fetrow, one would more fairly conclude that this reference teaches that sequence-based approaches to protein-function prediction can often, perhaps in most instances, be used *successfully*. It is difficult to apply the teachings of the Skolnick and Fetrow reference directly to the nectin polypeptides of the present application, because Skolnick and Fetrow were assessing prediction of protein function either across all classes of protein structures or to particular types of enzymes, but when read in its entirely this reference certainly *cannot* be considered to teach an inability of the skilled artisan to predict the functionality of nectin-3 polypeptide variants from their amino acid sequence, especially when nectin-3 function (inhibiting endothelial cell migration) has already been experimentally established for polypeptides comprising nectin-3 amino acid sequences.

The Metzler reference (Metzler *et al.*, 1997, *Nature Struct Biol* 4: 527-531) was discussed by Applicants in the June 2003 Response but will be discussed further here, because the Office Action of October 2003 again conclusorily cited Metzler, this time as demonstrating that "a single amino acid substitution or *what appears to be an inconsequential chemical modification* will often dramatically affect the biological activity and characteristic of a protein" (page 6 of the Office Action, emphasis added). Applicants respectfully submit that this statement of the Office Action mischaracterizes the teaching of the Metzler reference, and suggests that Metzler teaches unpredictability of the art, when it in fact teaches the opposite. There is no evidence that single amino acid substitutions, as shown in Table 2

at page 530 of the Metzler reference, would appear to one of skill in the art as "*inconsequential chemical modification[s]*". The Table 2 substitutions of the Metzler reference were made in amino acid residues that are either conserved among CTLA4 species homologues as shown in Figure 2 of Metzler, or are conserved among both CTLA4 *and* CD28 species homologues. Both CTLA4 and CD28 bind to CD80 and to CD86. Because of the art-recognized relationship between evolutionary amino acid sequence conservation and functional importance (as discussed above in reference to Skolnick and Fetrow), CTLA4 residues conserved among all CTLA4 and CD28 family members would be considered by the skilled artisan to be likely to be related to the CD80 and CD86 binding functions of CTLA4, and substitutions in these amino acids would not be considered as "*inconsequential chemical modification[s]*", but rather as having the potential to affect the activity of the polypeptide. And in fact a careful comparison of Table 2 with Figure 2 of Metzler reveals a clear correlation between the degree to which a residue is conserved in the Figure 2 alignment, and therefore its expected functional importance, and the effect that changing that residue has on the function of the polypeptide, as shown in Table 2. For example, CTLA4 residues E31, R33, E46, and K95 are completely conserved in all the sequences in the Figure 2 alignment, and mutation of these residues abolished or reduced binding of CTLA4 to CD80 and CD86. Once again, a thorough analysis of the Metzler reference shows that *it teaches the ability of the artisan to predict the function of polypeptide variants based on comparisons of amino acid sequences*.

The Office Action discusses a newly cited reference, Martinez *et al.*, 2001, *J Virology* 75(22): 11185-11195 that involves the characterization of the HSV entry activity of human and murine nectin-2 polypeptides. Martinez discloses that the HSV entry activity of human nectin-2 is abolished by the replacement of a particular human nectin-2 amino acid with a mouse amino acid (the M89F mutation). The Office Action mistakenly concludes from the Martinez reference that "it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences" (Office Action, page 6). In fact, the Martinez reference teaches the ability of the skilled artisan to predict the functional importance of polypeptide residues based on amino acid sequence comparisons. According to the Martinez reference (page 11185, bottom of column 1 and top of column 2), human and murine nectin-1 have HSV entry activity, and human nectin-2 has entry activity for HSV-2 and certain HSV-1 strains, but murine nectin-2 does *not* have entry activity for HSV strains. Previous studies had shown that the interaction of nectin-1 and human nectin-2 with HSV occurs through the V domain (Martinez, 11186 first column), therefore it was *expected* by the authors that segments of the human nectin-2 V domain would

confer HSV entry activity to mouse nectin-2, and conversely, that replacement of certain residues in the human nectin-2 V domain with residues from murine nectin-2, which has no HSV entry activity, would abolish the human nectin-2 HSV entry activity! Once again, there is a correlation between amino acid sequence conservation and importance for biological activity, as demonstrated by Martinez and Exhibit 1 submitted herewith. Exhibit 1 shows an alignment of the human and murine nectin-1 and nectin-2 amino acid sequences, and indicates the A and B segments of the human nectin-2 V domain that the Martinez authors identified as sufficient to confer the HSV entry activity on murine nectin-2 (page 11188, bottom of column 2, and Figure 3A). Within the A and B segments, there are only two amino acids that are shared by the polypeptides that have HSV entry activity (human and murine nectin-1, and human nectin-2), but *not* by murine nectin-2 that lacks HSV entry activity: the M89 and S92 residues of the human nectin-2 sequence. Thus, these residues would be regarded by the artisan as correlated with HSV entry activity and potentially important for HSV entry activity, and this prediction was confirmed experimentally for the M89 residue (Figure 9 of the Martinez reference). It is clear that, in contrast to the assertions of the Office Action, *the Martinez reference provides evidence of the ability of the skilled artisan to use amino acid sequence information to predict biological function of polypeptide variants.*

Therefore, none of these references cited by the Office Action provide support for the rejection of the claims on the basis that they purportedly lack enablement.

(3). The Office Action, at page 7, also cites *Colbert v. Lofdahl*, 21 USPQ2d, 1068 (BPAI 1992), but it is unclear what relevance this case has to the present rejection of the claims on the basis of an asserted lack of enablement. In *Colbert v. Lofdahl*, the issue was whether physical importation into the United States of bacteria plates containing a clone having protein A activity was sufficient to establish conception of the invention (a recombinant DNA molecule encoding protein A). In the present application, Applicants have provided nectin-3 amino acid sequences, and have provided guidance (as conceded by the Office Action) in how to make and use functional variants of these amino acid sequences. The Examiner is respectfully requested either to withdraw this basis for the rejection, or to explain with particularity how this case supports the rejection of the claims for an asserted lack of enablement.

For at least the above reasons, the rejection of claims 59-111 under 35 U.S.C. §112, first paragraph (enablement), has been traversed, and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 59-111 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not being described in the specification. This rejection is traversed for at least the reasons presented below.

The basis for rejection, as described at page 8 and particularly at the top of page 9 of the Office Action, appears to be directed at variants of the nectin-3 polypeptides of the invention. Applicants can find no clear basis for applying this rejection to claims 59-78, such claims being directed to polypeptide sequences that have been shown to possess the nectin-1 binding properties referred to (see, for example, Examples 4 through 6 at pages 53-56 of the specification). Applicants respectfully request that the rejection be withdrawn with respect to claims 59-78, or that the Examiner provide the basis for applying the rejection to these claims.

The Office Action supports the rejection of the claims with the conclusory statement on page 9, that "there is no described or art-recognized correlation or relationship between the structure of the invention, the nectin-3 extracellular domain, and it's inhibition of endothelial cell migration, the feature deemed essential to the instant invention". However, this statement by the Office Action is misplaced because it does not take into account the teaching of the specification concerning nectin structure and function.

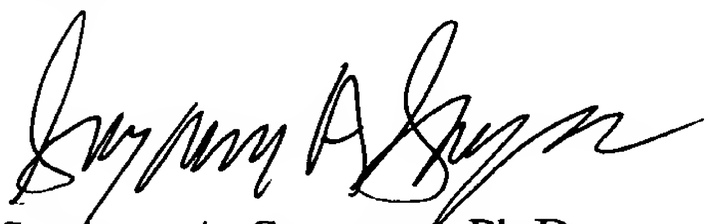
The specification teaches how the structures of the nectin-3 extracellular domain are related to binding interactions with other molecules, and how these binding interactions are involved in biological processes such as endothelial cell migration. The specification teaches, for example, that the extracellular domain of nectin-3 polypeptides contains Ig domains, particularly the N-terminal V-type Ig domain, important for its ability to bind other nectins: "The N-terminal Ig domain of nectin-1 and nectin-2 is a V-type Ig domain, while the two C-terminal Ig domains are C2-type domains. The N-terminal Ig domain of this family of molecules has been shown to be required for binding in *trans* to other nectin molecules on adjacent cells in a hetero- or homotypic fashion." (Page 4, lines 6-9.) "[I]nteraction of nectin polypeptides via their extracellular domains is involved in the movement or migration of epithelial and endothelial cells both in normal wound healing and in abnormal conditions such as restenosis." (Page 12, lines 26-28.) "Because the extracellular domain of nectin polypeptides binds to binding partners such as nectins and viral proteins, the extracellular domain, when expressed as a separate fragment from the rest of a nectin polypeptide, or as a soluble polypeptide fused, for example, to an immunoglobulin Fc domain, is expected to

disrupt the binding of nectin polypeptides to their binding partners." (Page 11, lines 27-31.) Therefore, in contrast to the assertion of the Office Action, the specification *does* teach a relationship "between the structure of the invention, the nectin-3 extracellular domain, and its inhibition of endothelial cell migration".

For at least the above reasons, the rejection of claims 59-111 under 35 U.S.C. §112, first paragraph (written description) is without basis; withdrawal of this rejection is respectfully requested.

If a telephone interview would be helpful in advancing the prosecution of this application, Applicants' attorney invites the Examiner to contact her at the number provided below.

Respectfully submitted,



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Seattle, WA 98119

Appendix A
U.S. Serial No. 09/972,268
Clean Version of Table 2 as of March 2004

Table 2
Conserved Nectin Amino Acids

(Hs=Homo sapiens)
(Mus=Murine)

```
HUNECTIN2 (SEQ ID NO:22)  ~~~~~~~~~~ ~~~~~~~~~~ MARAAALLPS RSPPTPLLWP LLLLLLL...
HUCD155   (SEQ ID NO:25)  ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ MARAMAAAWP LLLVALLVLS
HUNECTIN1 (SEQ ID NO:20)  ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~MARMG LAGAAGRWWG L...ALGLTA
HUNECTIN3 (SEQ ID NO:6)   MARTLRPSPL CPGGGKAQLS SASLLGAGLL LQPPTPPPLL LLLFPLLLFS
HUNECTIN4 (SEQ ID NO:24)  ~~~~~~~~~~ ~~~~~~~~~~ ~~~~MPLSLG AEMWGPEAWL LLLLLLASFT
consensus                                                    P  W  LLL  LL
```

```
                                                                        100
HUNECTIN2  ..ETGAQDVR VQVLPEVRGQ LGGTVELPCH L.LPPVPGLY ISLVTWQRPD
HUCD155    WPPPGTGDVV VQAPTQVPGF LGDSVTLPCY LQVPNMEVTH VSQLTWAR..
HUNECTIN1  FFLPGVHSQV VQVNDSMYGF IGTDVVLHCS FANP.LPSVK ITQVTWQK.S
HUNECTIN3  RLCGALAGP. IIVEPHVTAV WGKNVSLKCL I..EV..NET ITQISWEKIH
HUNECTIN4  GRCP..AGE. LETSDVVTVV LGQDAKLPCF YRGDS..GEQ VGQVAWARVD
              PG       VQV    V G   LG   V LPC      P         I QVTW R
```

```
                                                                        150
HUNECTIN2  APANHQNVAA FHPKMGPSFP SPKPGSERLS FVSAKQSTGQ DTEAELQDAT
HUCD155    .HGESGSMAV FHQTQGPSYS E....SKRLE FVAARLG...  ...AELRNAS
HUNECTIN1  TNGSKQNVAI YNPSMGVSV. .LAPYRERVE FL........  ..RPSFTDGT
HUNECTIN3  .GKSSQTVAV HHPQYGFSVQ ..GEYQGRVL FKNYSLN...  .......DAT
HUNECTIN4  AGEGAQELAL LHSKYGLHVS ..PAYEGRVE QPPPPRNPL.  .......DGS
                Q VA    HP   G SV       Y   RVE F                 DAT
```

```
                                                                        200
HUNECTIN2  LALHGLTVED EGNYTCEFAT FPKGSVRGMT WLRVIAKPKN QAEAQKVTF.
HUCD155    LRMFGLRVED EGNYTCLFVT FPQGSRSVDI WLRVLAKPQN TAEVQKVQL.
HUNECTIN1  IRLSRLELED EGVYICEFAT FPTGNRESQL NLTVMAKPTN WIEGTQAVLR
HUNECTIN3  ITLHNIGFSD SGKYICKAVT FPLGNAQSST TVTVLVEPTV SLIKGPDSLI
HUNECTIN4  VLLRNAVQAD EGEYECRVST FPAGSFQARL RLRVLVPPLP SLNPGP.ALE
             L   L   ED EG Y C F T FP GS        LRVLAKP N    E      L
```

```
                                                                        250
HUNECTIN2  ....SQDPTT VALCISKEGR PPARISWLSS LDWEAKETQV SGTLAGTVTV
HUCD155    ....TGEPVP MARCVSTGGR PPAQITWHSD LGGMPNTSQV PGFLSGTVTV
HUNECTIN1  AKKGQDDKVL VATCTSANGK PPSVVSWETR LKGEARVPGD SGTPMAPVTV
HUNECTIN3  DGGNE...TV AAICIAATGK PVAHIDWEGD LGEM..ESTT TSFPNETATI
HUNECTIN4  EGQGL...TL AASC.TAEGS PAPSVTWDTE VKGT..TSSR SFKHSRSAAV
                      T   A C SA G  PPA I W     L G     S    SG     TVTV
```

```
                                                                        300
HUNECTIN2  TSRFTLVPSG RADGVTVTCK VEH..ESFEE PALIPVTLSV RYPPEVSISG
HUCD155    TSLWILVPSS QVDGKNVTCK VEH..ESFEK PQLLTVNLTV YYPPEVSISG
HUNECTIN1  ISRYRLVPSR EAHQQSLACI VNYHMDRFKE ....SLTLNV QYEPEVTIEG
HUNECTIN3  ISQYKLFPTR FARGRRITCV VKHP..ALEK DIRYSFILDI QYAPEVSVTG
HUNECTIN4  TSEFHLVPSR SMNGQPLTCV VSHP..GLLQ DQRITHILHV SFLAEASVRG
TS    LVPSR  A G   TC  V H    FE          L V  Y PEVSI G
```

```
                                                                        350
HUNECTIN2  Y.DDN.WYLG RTDATLSCDV RSNPEPTGYD WSTTSGTFPT SAVAQGSQLV
HUCD155    Y.DNN.WYLG QNEATLTCDA RSNPEPTGYN WSTTMGPLPP FAVAQGAQLL
HUNECTIN1  F.DGN.WYLQ RMDVKLTCKA DANPPATEYH WTTLNGSLPK GVEAQNRTLF
HUNECTIN3  Y.DGN.WFVG RKGVNLKCNA DANPPPFKSV WSRLDGQWPD GLLASDNTLH
HUNECTIN4  LEDQNLWHIG REGAMLKCLS EGQPPPSYN. WTRLDGPLPS GVRVDGDTLG
Y D N WYLG R  A L C A   NPPPT Y  WSTL G LP  G  AQG TL
```

```
                351                                                        400
HUNECTIN2       IH.AVDSLFN TTFVCTVTNA VGMGRAEQVI FVRETP.... ..........
HUCD155         IR.PVDKPIN TTLICNVTNA LGARQAELTV QVKEGP.... ..........
HUNECTIN1       FKGPINYSLA GTYICEATNP IGTRSGQVEV NITEFPYTPS ..........
HUNECTIN3       FVHPLTFNYS GVYICKVTNS LGQRSDQKVI YISDPPTTTT LQPTIQWHPS
HUNECTIN4       F.PPLTTEHS GIYVCHVSNE FSSRDSQVTV DVLDPQEDSG KQ........
                F  P       GTYIC VTN   G R  Q  V  V E P

                401                                                        450
HUNECTIN2       .......... .......RAS P...RDV..G PLVWGAVGGT LLVLLLLAGG
HUCD155         .......... .......PSE H...SGISRN AIIFLVLG.. ILVFLILLGI
HUNECTIN1       .......... .......PPE HGRRAGPVPT AIIGGVAGSI LLVLIVVGGI
HUNECTIN3       TADIEDLATE PKKLPFPLST LATIKDDTIA TIIASVVGGA LFIVLVSVLA
HUNECTIN4       ....VDLV.. .......... .......SAS VVVVGVIAAL LFCLLVVVVV
                                                 II GV G   LLVLLV  G

                451                                                        500
HUNECTIN2       SLAFILLRVR RR.....RKS .PGGAGGGAS GDGGFYDPKA QVLGNGDPVF
HUCD155         GIYFYWSKCS REVLWHCHLC .PSSEHHQSC RN~~~~~~~~ ~~~~~~~~~~
HUNECTIN1       VVALRRRRHT FKGDYSTKKH .VYGNGYSKA GIPQHHPPMA QNLQYPDDSD
HUNECTIN3       GIFCYRRRRT FRGDYFAKNY IPPSDMQKES QIDVLQQDEL D..SYP.DSV
HUNECTIN4       LMSRYHRR.. .KAQQMTQKY EEELTLTREN SIRRLHSHHT DPRSQPEESV
                    Y RR                P           I                P  S

                501                                                        550
HUNECTIN2       WTPVVPGPME P.DGKDEEEE EEEEKAEKGL MLPPPPALED DMESQLDGSL
HUCD155         ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~
HUNECTIN1       .DEKKAGPLG G.SSYEEEEE EEEGGGGGER KVGGPHPKYD EDAKRPYFTV
HUNECTIN3       .KKENKNP.. .VNNLIRKDY LEEPEKTQWN NVENLNRFER PMDYYEDLKM
HUNECTIN4       GLRAEGHPDS LKDNSSCSVM SEEPEGRSYS TLTTVREIET QT...ELLSP
                       P                EE                E

                551                                                        597
HUNECTIN2       ISRRAVYV~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~
HUCD155         ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~
HUNECTIN1       DEAEARQDGY GDRTLGYQYD PEQLDLAENM VSQNDGSFIS KKEWYV~
HUNECTIN3       GM.KFVSDEH YDENEDDLVS HV...DGSVI SR...REWYV ~~~~~~~
HUNECTIN4       GSGRAEEEED QDEGIKQAMN HFVQENGTLR AKPTGNGIYI NGRGHLV
                    A       D
```

Exhibit 1

```
                1                                                    50
Nec-1 human     MARmq.Laqa aqrwwqLaLq LtaffLpqvh sQvVqVn..d smyGfiGtdV
Nec-1 mouse     MARmq.Laqa aqrwwqLaLq LtaffLpqTh tQvVqVn..d smyGfiGtdV
Nec-2 human     MARaaaLlps rspptpLlwp LlllllleTq aQdVrVqvlp evrGqlGqtV
Nec-2 mouse     MARaavLpps rlsptlplLp LlllllqeTq aQdVrVrvlp evrGrlGqtV
   Consensus    MAR---L--- ------L-L- L----L--T- -Q-V-V---- ---G--G--V

                                                <--A--->      <-B-->
                51                                                  100
Nec-1 human     vLhCsfanPl PsvkItQVTW Qk.stnqskQ NVAiynPsMG VSvlaPy..r
Nec-1 mouse     vLhCsfanPl PsvkItQVTW Qk.asnqskQ NmAiynPtMG VSvlpPy..e
Nec-2 human     eLpChllpPv PqlyIslVTW Qrpdapanhq NVAafhPkMG pSfpsPkpgs
Nec-2 mouse     eLpChllpPt te.rvsQVTW Qrldqtv... .VAafhPsfG Vdfpnsqfsk
   Consensus    -L-C----P- P---I-QVTW Q--------Q NVA---P-MG VS---P----
                                                          ↑  ↑

                101                                                 150
Nec-1 human     eRveFlR... .......psf tDqTirLsrL elEDEGvYiC EFATFPtGnR
Nec-1 mouse     kRveFlR... .......psf iDqTirLsGL elEDEGmYiC EFATFPtGnR
Nec-2 human     eRlsFvsakq stqgdteael qDaTlaLhGL tvEDEGnYtC EFATFPkGsv
Nec-2 mouse     dRlsFvRar. ...petnadl rDaTlafrGL rvEDEGnYtC EFATFPnGtR
   Consensus    -R--F-R--- ---------- -D-T--L-GL --EDEG-Y-C EFATFP-G-R

                151                                                 200
Nec-1 human     esqlnLtVmA KPtNwiEgtq avlrakkgqd dkVlVAtCtS anGkPPsvvS
Nec-1 mouse     esqlnLtVmA KPtNwiEqtr avlrarkgqd nkVlVAtCtS anGkPPsavS
Nec-2 human     rqmtwLrViA KPkNqaEaqk vtf.....sq dpttVAlCiS keGrPPariS
Nec-2 mouse     rqvtwLrViA qPeNhaEaqe vti.....qp qsVaVArCvS tgGrPParit
   Consensus    -----L-V-A KP-N--E--- ---------- --V-VA-C-S --G-PP---S

                201                                                 250
Nec-1 human     WetrLkGEA. EyQEirnpnG TVTVISRYrL VPSreAhqqs laCiVnyhmd
Nec-1 mouse     WetrLkGEA. EyQEirnpnG TVTVISRYrL VPSreAhrqs laCiVnyhld
Nec-2 human     WlssLdwEAk EtQvsqtlaG TVTVtSRftL VPSqrAdqvt vtCkVeh..e
Nec-2 mouse     WissLqGEAk dtQEpqiqaG TVTiISRYsL VPvqrAdqvk vtCrVeh..e
   Consensus    W---L-GEA- E-QE-----G TVTVISRY-L VPS--A---- --C-V-----

                251                                                 300
Nec-1 human     rFkE....sl TLnVqYePEV tIeGfDgNWY LqRmDvkLTC kadaNPpaTe
Nec-1 mouse     rFrE....sl TLnVqYePEV tIeGfDgNWY LqRtDvkLTC kadaNPpaTe
Nec-2 human     sFeEpalipv TLsVrYpPEV sIsGyDdNWY LqRtDatLsC dvrsNPepTq
Nec-2 mouse     sFeEpillpv TLsVrYpPEV sIsGyDdNWY LqRseaiLTC dvrsNPepTd
   Consensus    -F-E------ TL-V-Y-PEV -I-G-D-NWY L-R-D--LTC ----NP--T-

                301                                                 350
Nec-1 human     YhWtTlnGsl PkqveAQnrt Lffkqpinys laqTyICeAT NpiGTrsqqv
Nec-1 mouse     YhWtTlnGsl PkqveAQnrt Lffrqpitys laqTyICeAT NpiGTrsqqv
Nec-2 human     YdWsTtsGtf PtsavAQqsq Lviha.vdsl fntTfvCtvT NavGmqraeq
Nec-2 mouse     YdWsTtsGvf PasavAQqsq Llvhs.vdrm vntTfICtAT NavGTqraeq
   Consensus    Y-W-T--G-- P----AQ--- L--------- ---T-IC-AT N--GT-----

                351                                                 400
Nec-1 human     evnitEfPyt psppehqRrA .pvptaIIGC vaqsiLLvli vvqGIvvalr
Nec-1 mouse     evnitEfPyt pt.pehqRrA .qmptaIIGG vaqsvLLvli vvqGIivalr
Nec-2 human     vifvrEtPra sp.....Rdv .plvwqavGC tllvlLLlaq qslafillrv
Nec-2 mouse     vilvrEsP.. st.....aqA ..atqqIIGC iiaaiiatav aqtGIlicrq
   Consensus    -----E-P-- -------R-A -----II-G- -----LL--- ---GI-----
```

```
                401                                                 450
Nec-1 human     RRRhtfkGdy stkkhvyGng Ys.KAgiPqh hpPmaqnlqy Pddsddekka
Nec-1 mouse     RRRhtfkGdy stkkhvyGng Ys.KAgiPqh hpPmaqnlqy Pddsddekka
Nec-2 human     RRRrkspGqa gqgasgdGgf YdpKAqvlgn gdPvfwtpvv Pgpme.....
Nec-2 mouse     qRkeqrlqaa deeeeleG.. ..ppsykPpt pkakleepem Psqlf.....
   Consensus    RRR----G-- -------G-- Y--KA--P-- --P------- P---------

                451                                                 500
Nec-1 human     gPLGgSsyEE EEEEEEgqgg Gerkvgqphp kYdEdakrPy ftvDeaEarq
Nec-1 mouse     sPLGgSsy.E EEEEEEgqgg Gerkvgqphp kYdEdakrPy ftvDeaEarq
Nec-2 human     .PdGkd..EE EEEEEEkaek Glm.....lP ...p....Pp aleDdmEsql
Nec-2 mouse     .tLGaS..Eh spvktpyfda Gvscadqemp rYhE....lp tleersgpll
   Consensus    -PLG-S--EE EEEEEE---- G--------P -Y-E----P- ---D--E---

                501                                                 550
Nec-1 human     DGygdrtlgy qydPeqldla enmvSqnDgs fiskkEwyv~ ~~~~~~~~~~
Nec-1 mouse     DGygdrtlgy qydPeqldla enmvSqnDgs fiskkEwyv~ ~~~~~~~~~~
Nec-2 human     DGslisrrav yv~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~ ~~~~~~~~~~
Nec-2 mouse     lGatglgpsl lvpPgpnvve qvslSleDee eddeeEdfld kinpiydals
   Consensus    DG-------- ---P------ ----S--D-- -----E---- ----------

                551                 571
Nec-1 human     ~~~~~~~~~~ ~~~~~~~~~~ ~
Nec-1 mouse     ~~~~~~~~~~ ~~~~~~~~~~ ~
Nec-2 human     ~~~~~~~~~~ ~~~~~~~~~~ ~
Nec-2 mouse     ypspsdsyqs kdffvsramy v
   Consensus    ---------- ---------- -
```